UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/765,324	12/24/96	KOREN E	OMRF143-CIP2

HM12/0130

PATREA L PABST
ARNALL GOLDEN & GREGORY
2800 ONE ATLANTIC CENTER
1201 WEST PEACHTREE STREET
ATLANTA GA 30309-3450

EXAMINER	
DUFFY, P	
ART UNIT	**PAPER NUMBER**
1645	20

DATE MAILED: 01/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/765,324	Koren et al.
Examiner	**Group Art Unit**
Duffy	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P ri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 11-8-00.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp siti n of Claims

☒ Claim(s) 48-51 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 48-51 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Applicati n Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Revi w, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other_____

Office Action Summary

Response to Amendment

1. The amendment filed 11-8-00 has been entered into the record. Claims 20, 21 and 35-37 have been canceled. Claims 48-51 are pending and under examination. It is again noted that the submitted amended claim 43 has been renumbered as 48 pursuant to Rule 126 because claim numbers 43-48 already existed in the prosecution history of this application.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. Any rejection not reiterated herein is withdrawn based on applicants amendments.

Rejections Maintained

Priority

4. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be updated in this application. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Specification

5. The title and abstract of the invention is not descriptive of the claimed inventions. A new title and abstract are required that is clearly indicative of the invention to which the claims are directed. This objection was not addressed by Applicants' representative.

Claim Rejections - 35 USC § 112

6. Claims 48-51 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants arguments have been carefully considered but are not fully persuasive. The only method conceived of in the instant specification of separation of self aggregated and degraded material from the preserved ApoB protein (the delipidized, reduced and carboxymethylated ApoB-100 is a polyacrylamide gel containing 8 M urea. Applicants therefore conceived of a single method of purification, polyacrylamide gel containing 8 M urea. Applicants argue that many methods to remove aggregates are known to the art and the claims have not been so limited because of this. This is not persuasive, the written description does not convey that the alleged alternatives were conceived by Applicants at the time of filing. Applicants point to the specification at page 43 for generic support. This is not persuasive, the passages at page 43 are drawn to the use of antibodies for purification of LDL from plasma. Applicants are attempting to mix and match concepts presented in the specification to broaden the claims. Such mixing and matching of concepts does not convey that Applicants had conceived the claimed invention at the time of filing. The passages nor the specification convey the argued concept that the immunogen is critical and that methods of using the immunogen were broadly part of the invention at the time the invention was filed. The specific passage that supports a method of making a monoclonal antibody with a particular immunogen is not seen to support the conception of the immunogen for broadly making any antibody. Applicants argue that support for monoclonal antibodies inherently provides support for making polyclonal antibody. This is not so,

the passage to which applicants point does not conceive of the use of the immunogen to make polyclonal antibodies, only monoclonal antibodies to a particular immunogen processed in a particular manner.

The rejection is maintained.

7. Claims 48-51 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a monoclonal antibody which specifically binds a stable, conformationally independent epitope which is uninfluenced by the lipid content of an apolipoprotein and lipoprotein, comprising: (a) immunizing an animal with a delipidized, soluble, reduced, carboxymethylated and electrophoretically purified apolipoprotein; (b) producing hybridomas from a spleen isolated from the immunized animal; and (c) screening for a monoclonal antibody which specifically binds a stable, conformationally independent epitope which is uninfluenced by the lipid content of an apolipoprotein and lipoprotein, it does not reasonably provide enablement for generically antibodies (i.e. polyclonal and monoclonal) or immunizing with an lipoprotein which has been dilapidated, reduced, solubilized and purified. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Applicants' arguments have been carefully considered but are not persuasive. Applicants appears to argue the examiner has not set forth and has not provided any art or basis for the rejection and that the specification clearly enables all in light of the general applicability of the methodology and should not be so limited. This argument is not understood the basis has been clearly set forth in the rejection of record and art provided. Applicants remind the examiner of an interview on the parent case in which these issues were resolved. A review of the record in the parent applicants demonstrates that the claimed inventions are different. Additionally, the claims

of the parent are limited to monoclonal antibodies and the claims in the parent were originally filed, the instant claims are not originally filed and are not limited to monoclonal antibodies. The scope of the allowed claims is not in issue. The scope of claims newly added and not directed to the same invention remain an issue. The decision for originally presented claims of different scope is not binding on this application drawn to a different method, a method that has no support in the originally filed claims but only finds support in brief textual sections of the specification.

The rejection is maintained.

8. Claims 48- 51 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons made of record in Paper No. 23, mailed 5-5-00.

As to claims 48, 49, and 51, the claims are confusing because dilapidated lipoprotein are no longer lipoproteins per se and thus it is unclear what composition is administered, what is purified from the dilapidated, reduced, solubilized lipoprotein. Or is the lipoprotein first purified, then dilapidated and reduced ? Is not a lipoprotein already soluble in plasma ? The passage which applicants point to in the specification do not provide guidance as to the metes and bounds of these terms as it applies to lipoproteins. It is unclear how and what is obtained from such. This rejection is not addressed by Applicants' representative.

Claims 48-51 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims are drawn to a method of making an antibody, however the method never achieves the goal of the preamble. The omitted steps are at least: (b) producing hybridomas from a spleen isolated from the immunized animal; and (c) screening for a monoclonal antibody

which specifically binds a stable, conformationally independent epitope which is uninfluenced by the lipid content of an apolipoprotein and lipoprotein. Applicants indicate that the critical step in making an antibody is the immunization with the claimed immunogen, where the invention resides in the treatment of the immunogen that is critical to the production of antibodies. This is not persuasive, the fact that the alleged critical element is in the claims, does not obviate that other critical elements are missing from the claims. Applicants are not claiming a method of immunization but a method of making antibodies and no antibodies are in fact produced or isolated. The claims remain incomplete for reasons made of record.

New Rejections Based on Amendment

9. Claims 48, 50 and 51 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Lee et al (Biochimia et a Biophysica Acta, 666:133-146, 1981).

Lee et al teach isolated lipoprotein LDL_2 were dilapidated wet with ethanol and diethyl ether, the dilapidated LDL_2 were solubilized in 6M guanidine-HCl buffer containing the reducing agent dithiothreitol, after carboxymethylation the reduced and carboxymethylated (RCM) LDL_2 apolipoprotein was purified by gel filtration to yield pure RCM apolipoprotein B (see abstract page 133 and page 135, column 2, to page 146, column 2). Lee et al teach the production of antisera using the purified RCM apolipoprotein B (see page 136, column 2, "Preparation of Antisera"). As such the apolipoprotein of Lee et al has been dilapidated, reduced, solubilized, carboxymethylated and the dilapidated reduced solubilized and carboxymethylated apolipoprotein B (RCM) was subsequently further purified. Since Apo B is inherently contained in LDL_2 and the specification/claims are unclear as to what the immunogen consists of, the method as it relates to lipoproteins is also deemed anticipated.

As such the immunogen and method of Lee anticipate the instant claims.

10. Claims 48, 49, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (Biochimia et a Biophysica Acta, 666:133-146, 1981) in view of Gooding, J.W., (in Monoclonal Antibodies, Academic Press Inc., Orlando, Florida, 1983, p 56-97).

Lee et al is set forth *supra*. Lee et al differs by not making a monoclonal antibody by isolating the spleen from the immunized animal, making hybridomas and screening for binding to the desired apolipoprotein or lipoprotein.

Gooding teaches methods of production of monoclonal antibodies, immunization of an animal (section 3.2), preparation of spleen cells from the immunized animal (section 3.5), preparation of myeloma cells (section 3.6), fusion protocols to make hybridomas (section 3.8), and screening assays (3.10.2--3.10.10) to screen for antigen binding and subsequent cloning of hybridomas secreting antibodies which bind the antigen of interest.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to make a monoclonal antibody which binds a dilapidated, reduced, solubilized, carboxymethylated and purified RCM Apo B of Lee et al, by substituting the RCM Apo B immunogen of Lee et al in the classical methods of Gooding because monoclonal antibodies provide the art recognized advantages of an unlimited supply of an identical detection reagent, reduce interassay variability and increase assay reproducibility.

11. Claims 48, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (Biochimia et a Biophysica Acta, 666:133-146, 1981) in view of Zhou et al (Acta Acad Med Hubei, 11(4):298-302, 1990) and Mills et al (in Laboratory Techniques in biochemistry and molecular biology, a guidebook to lipoprotein technique, Elsevier, 1984, pages 384-448)

Lee et al is set forth *supra*. Lee et al differs by not dilapidated, reduced, solubilized, carboxymethylated and purified Apo AI, Apo AII, Apo CIII and Apo E.

Zhou et al teach the purification of apolipoprotein A-I (Apo A-I). Apo A-I was precipitated by heparin-citrate buffer (i.e. the instant purified), dilapidated with acetone-ethanol (i.e. the instant dilapidated), dissolved in Tris-Urea Buffer (i.e. solubilized), subjected to SDS-polyacrylamide gel electrophoresis (i.e. the instant reduction and purification) and elution the gels with SDS-Tris buffer. Zhou et al produces antisera against Apo A-I by immunizing with the dilapidated, reduced, solubilized and purified Apo A-I. Since, Apo A-I is present in high density lipoproteins (HDL), antibodies made by purified Apo A-I would also bind lipoproteins which are known to have Apo A-I present. Zhou et al teach that antibodies to Apo-AI and Apo B are useful in the screening for coronary heart disease.

Mills et al teaches the routine methods of isolation of purified soluble Apo AI, Apo AII, Apo CII and Apo E from plasma lipoproteins. Mills et al teach that monospecific antibodies to apolipoproteins are better suited to clinical use for immunoassay determination.

It would have been *prima facie* obvious to one having ordinary skill in the art to isolate Apo AI, Apo AII, Apo CII and Apo E from plasma lipoproteins according to Mills et al and further delipidate, reduce, solubilize and purify the apolipoproteins according to Lee et al because Lee et al teach that a purified, solubilized, dilapidated and reduced apolipoprotein is suitable as an immunogen to make antibodies. One would have been motivated to make antibodies to Apo AI, Apo AII, Apo CII and Apo E using the immunogen as modified supra because Zhou et al teach that antibodies to Apo AI and Apo B are useful in immunoassays for the differential diagnosis of coronary heart disease and Mills et al teach that apolipoprotein antibodies would be potentially useful and attractive in a clinical setting because the immunoassay is less time consuming.

Status of Claims

12. All claims stand rejected.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
January 29, 2001

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600